Copy for the designated Office (DO/US)

PCT/US00/18747

PATENT COOPERATION TREATY

10/018599

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

To:

PIERCE, N., Scott
Hamilton, Brook, Smith & Reynolds
P.O. Box 9133
Concord, MA 01742-9133
ETATS-UNIS D'AMERIQUE

Date of mailing (day/month/year) 03 December 2001 (03.12.01)	
Applicant's or agent's file reference 1161.1027032	**IMPORTANT NOTIFICATION**
International application No. PCT/US00/18747	**International filing date** (day/month/year) 07 July 2000 (07.07.00)

1. The following indications appeared on record concerning:

☐ the applicant ☐ the inventor ☒ the agent ☐ the common representative

Name and Address

PIERCE, N., Scott
Hamilton, Brook, Smith & Reynolds, P.C.
Two Militia Drive
Lexington, MA 02421
United States of America

State of Nationality:

State of Residence:

Telephone No.: 781 861 6240

Facsimile No.: 781 861 9540

Teleprinter No.:

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☐ the person ☐ the name ☒ the address ☐ the nationality ☐ the residence

Name and Address

PIERCE, N., Scott
Hamilton, Brook, Smith & Reynolds
P.O. Box 9133
Concord, MA 01742-9133
United States of America

State of Nationality:

State of Residence:

Telephone No.: 978 341 0036

Facsimile No.: 978 341 0136

Teleprinter No.:

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

☒ the receiving Office
☐ the International Searching Authority
☐ the International Preliminary Examining Authority
☒ the designated Offices concerned
☐ the elected Offices concerned
☐ other:

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland** Facsimile No.: (41-22) 740.14.35	Authorized officer Ki-Nam HA Telephone No.: (41-22) 338.83.38

Form PCT/IB/306 (March 1994)

004505237

Copy for the Elected Office (EO/US)

PCT/US00/18747

PATENT COOPERATION TREATY

10/018,599

PCT

From the INTERNATIONAL BUREAU

To:

PIERCE, N., Scott
Hamilton, Brook, Smith & Reynolds,
P.C.
530 Virginia Road
P.O. Box 9133
Concord, MA 01742-9133
ETATS-UNIS D'AMERIQUE

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and
Administrative Instructions, Section 422)

Date of mailing (day/month/year) 28 February 2002 (28.02.02)	
Applicant's or agent's file reference 1161.1027032	**IMPORTANT NOTIFICATION**
International application No. PCT/US00/18747	**International filing date** (day/month/year) 07 July 2000 (07.07.00)

1. The following indications appeared on record concerning:

☐ the applicant ☐ the inventor ☒ the agent ☐ the common representative

Name and Address

PIERCE, N., Scott
Hamilton, Brook, Smith & Reynolds
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Concord, MA 01742-9133
United States of America

State of Nationality:

State of Residence:

Telephone No.: 978 341 0036

Facsimile No.: 978 341 0136

Teleprinter No.:

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☐ the person ☒ the name ☒ the address ☐ the nationality ☐ the residence

Name and Address

PIERCE, N., Scott
Hamilton, Brook, Smith & Reynolds,
P.C.
530 Virginia Road
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Concord, MA 01742-9133
United States of America

State of Nationality:

State of Residence:

Telephone No.: 978 341 0036

Facsimile No.: 978 341 0136

Teleprinter No.:

3. Further observations, if necessary:

Corrected version: This form replaces the Form PCT/IB/306 sent on 03 December 2001 (03.12.01).

4. A copy of this notification has been sent to:

☒ the receiving Office
☐ the International Searching Authority
☐ the International Preliminary Examining Authority
☐ the designated Offices concerned
☒ the elected Offices concerned
☐ other:

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland** Facsimile No.: (41-22) 740.14.35	Authorized officer Peter WIMMER Telephone No.: (41-22) 338.83.38

Form PCT/IB/306 (March 1994)

004693690

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Commissioner
US Department of Commerce
United States Patent and Trademark Office, PCT
2011 South Clark Place Room
CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 19 March 2001 (19.03.01)	
International application No. PCT/US00/18747	**Applicant's or agent's file reference** 1161.1027032
International filing date (day/month/year) 07 July 2000 (07.07.00)	**Priority date** (day/month/year) 07 July 1999 (07.07.99)
Applicant GAWRYL, Maria, S. et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

04 January 2001 (04.01.01)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

Olivia TEFY

Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION** see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
1161.1027032		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/US 00/ 18747	07/07/2000	07/07/1999
Applicant		
BIOPURE CORPORATION et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [ ] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. _____

   [ ] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure:

   [ ] because this figure better characterizes the invention.

   [X] None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 00/18747

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A01N1/02 A61M1/02 A01J1/00 A61J1/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A01N A61M A01J A61J

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, BIOSIS, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 691 452 A (GAWRYL MARIA S ET AL) 25 November 1997 (1997-11-25) * Column 2, lines 9-11, col. 3, lines 32-54, Example 2, lines 50-54 * ---	1-9
X	EP 0 083 778 A (FRESENIUS AG) 20 July 1983 (1983-07-20) * Page 5, lines 27-30, page 8, lines 4-17, page 9, line 24 to page 10, line 7 and 30 * ---	1-9
X	DE 39 15 252 A (FRESENIUS AG) 15 November 1990 (1990-11-15) * Column 1, lines 55-60, col. 4, lines 45-60 * --- -/--	1-9

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
31 October 2000	14/11/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Faizi, R

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	DE 296 05 214 U (SENGWALD VERPACKUNGEN GMBH) 4 September 1997 (1997-09-04) * Page 1, lines 1-7, page 3, lines 12-15, page 7, lines 16, 31-33, page 8, line 12 *	1-9
Y	GB 2 107 191 A (ALZA CORP) 27 April 1983 (1983-04-27) * Page 8, line 33 to 48, 110-112 *	1-9
Y	DE 76 21 615 U (BIOTEST SERUM INSTITUT GMBH) 3 February 1977 (1977-02-03) * the whole document *	1-9
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 00/18747

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 00/18747

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COPY

INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY (IPEA)

International Application No.:	PCT/US00/18747
International Filing Date:	07 July 2000
Applicant:	Biopure Corporation
Receiving Office:	RO/US
Priority Date Claimed:	07 July 1999
Attorney's Docket No.:	1161.1027032

REPLY TO FIRST WRITTEN OPINION

VIA FACSIMILE, CONFIRMATION COPY BY EXPRESS MAIL INTERNATIONAL

International Preliminary Examining
Authority (IPEA)
European Patent Office
D-80298 Munich, GERMANY

EL844445856US

Sir:

This is a reply to the First Written Opinion mailed from the International Preliminary Examining Authority on April 27, 2001 for the subject application.

In accordance with PCT Rule 66.8(a), replacement pages 40 - 41 are attached.

For the Examiner's convenience, the remainder of this reply is itemized under appropriate subheadings.

Cancellation of Claims and Substitution with New Claims

Independent Claims 1 and 6 have been cancelled and substituted with new Claims 1 and 6 on replacement pages 40-41. New Claims 1 and 6 make more clear that the transparent laminate material of the oxygen barrier film overwrap package includes a polyolefin layer and an oxygen barrier layer that includes ethylene vinyl alcohol. Support for new independent Claims 1 and 6 is found in cancelled Claims 1 and 6, and also in the

specification at page 3, lines 2-25 and at page 33, line 8 through page 34, line 12. No new matter has been added.

Applicant's Invention

Applicant's claimed invention is directed to a method for preserving a packaged deoxygenated hemoglobin blood substitute and to a preserved deoxygenated hemoglobin blood substitute. The method for preserving a packaged deoxygenated hemoglobin blood substitute includes maintaining the packaged deoxygenated hemoglobin blood substitute in an oxygen barrier film overwrap package. The oxygen barrier film overwrap package includes a transparent laminate material. The transparent laminate material includes a polyolefin layer and an oxygen barrier layer that includes ethylene vinyl alcohol. The transparent laminate material has a thickness of between about 0.0254 and 0.254 millimeters, and an oxygen permeability of less than about 0.01 cubic centimeters per 645 square centimeters over 24 hours at 1 atmosphere and at about 23°C.

The preserved deoxygenated hemoglobin blood substitute includes a packaged deoxygenated hemoglobin blood substitute and an oxygen barrier film overwrap. The oxygen barrier film overwrap package includes a transparent laminate material. The transparent laminate material includes a polyolefin layer and an oxygen barrier layer that includes ethylene vinyl alcohol. The transparent laminate material has an oxygen permeability of less than about 0.01 cubic centimeters per 645 square centimeters over 24 hours at 1 atmosphere and at about 23°C. The packaged deoxygenated hemoglobin blood substitute is sealed within the overwrap package.

Advantages of Applicant's Invention

Applicant's claimed invention has several advantages. For example, the overwrap is transparent, thereby allowing a label on the primary package containing the deoxygenated hemoglobin solution to be seen without manipulation of the overwrap. Further, the overwrap provides a barrier to atmospheric oxygen that, at normal temperatures, such as at normal room temperature, enables the deoxygenated hemoglobin blood substitute to be stored for extended periods. ("Room temperature" is defined in the

specification at page 3, line 10, to be about 23°C). In addition, the preserved deoxygenated hemoglobin blood substitute does not require the presence of materials, such as polyvinylidine chloride (PVD), that pose a medical waste problem by the presence of noxious chemicals, including polycyclic aromatic hydrocarbons and hydrochloric acids that are generated during incineration. Applicant's preserved deoxygenated hemoglobin blood substitute also enables visual inspection of the deoxygenated hemoglobin solution contained within the primary package without disturbing the overwrap. Therefore, the deoxygenated hemoglobin can be inspected for quality without risking rupture of protective packaging components.

Reasoned Statement under Rule 66.2(a)(ii) with Regard to Novelty, Inventive Step or Industrial Applicability

The Examiner stated that the subject matter of Claims 1-9 lack novelty and an inventive step in view of D1 (U.S. 5,691,452), D2 (EP 0083778), D3 (DE 3915252), D4 (DE 29605214), D5 (GB 2107191), and D6 (GM 7621615). In essence, the Examiner stated that: D1 addresses the problem of finding a material which satisfies the requirements of oxygen impermeability, disclosing the same parameters as at present; D2 requires that the bag be transparent in order to detect any changes, and for better handling; D3 puts an onus of the reduction of the oxygen permeability of the wall material; and that similar containers are known from D4 to D6. According to the Examiner, a skilled person, faced with the problems encountered by the present demand, would first apply the solution proposed by the prior art, before investing any further inventive activity. The Examiner stated that the present demand is thus not found to be based on an inventive step.

In contrast to the Examiner's statement, D1 does not disclose the same parameters as Applicant's claimed invention. For example, there is no disclosure in D1 of an overwrap that includes a transparent laminate having a polyolefin layer and an oxygen barrier layer that includes ethylene vinyl alcohol. For example, at Col. 3, lines 13-20, D1 teaches that foil laminates, which typically are not transparent, are preferred:

> In a preferred embodiment, a foil laminate is employed where the foil is an aluminum, silver, gold or other metal. The foil layer preferably has a thickness between about 0.0001 and 0.001 inches, more preferably about 0.003 inches. The laminate typically contains one or more polymeric layers. The polymer can be a variety of polymeric materials including, for example, a polyester layer (e.g. a 48-gauge polyester), polypropylene, nylon, etc.

None of the other references cited by the Examiner, taken either separately or in combination, remedy the deficiencies of reference D1, as applied to the claimed invention of the present Demand. In particular, none of the references cited by the Examiner, taken separately or in combination, disclose or suggest a transparent laminate that comprises a polyolefin layer and an oxygen barrier layer that includes ethylene vinyl alcohol. Further, none of the references cited by the Examiner, taken separately or in combination, disclose or suggest use of such a transparent laminate material as a component of an oxygen barrier film overwrap package to contain a packaged deoxygenated hemoglobin blood substitute.

Applicant has demonstrated in an example, set forth at page 33, line 8 through page 34, line 12 (Example 4), in the specification that an embodiment of the claimed invention preserves deoxygenated hemoglobin over a period of time and under conditions that are the equivalent of 24 months at 23°C. In particular, Example 4 of the specification is an embodiment of the claimed invention, wherein deoxygenated hemoglobin was stored in a primary package of polyethylene (2 mil) and nylon (2 mil). The primary package was overwrapped in a transparent laminate overwrap that included a layer of ethylene vinyl alcohol (i.e., ethylene vinyl alcohol copolymer) sealed between two layers of polypropylene. As described in Example 4, the deoxygenated hemoglobin blood substitute, packaged within the primary package and the transparent laminate overwrap, was stored at about 40°C in an atmosphere of about 60 percent relative humidity (RH) for a period of about 12 months. The concentrations of various components were measured initially, and at 3 month intervals through the 12 month period. The results are shown in Table 4 at page 34 of the specification. As can be seen at Table 4, the methemoglobin

content after 12 months approximated 7.9 percent. The measured amount of methemoglobin of 7.9 percent is significantly lower than the measurement that would have been obtained in the absence of the overwrap.

As discussed above, Applicant's claimed invention has several advantages. Specifically, the overwrap is transparent, thereby allowing a label on the primary package containing deoxygenated hemoglobin solution to be seen without manipulation of the overwrap. Further, the overwrap provides a barrier to atmospheric oxygen that, at normal temperatures, such as at normal room temperature, enables a deoxygenated hemoglobin blood substitute to be stored for extended periods of time. Also, the deoxygenated hemoglobin blood substitute can be observed visually without disturbing the overwrap. Further, the overwrap package does not include the presence of materials, such as polyvinylidine chloride, that pose a medical waste problem, such as generation of polycyclic aromatic hydrocarbons and hydrochloric acids during incineration.

No other references cited by the Examiner disclose or suggest use of an oxygen barrier film overwrap that employs a transparent laminate which, in turn, includes a polyolefin layer and a layer that includes ethylene vinyl alcohol. Further, none of the references cited by the Examiner disclose or suggest use of such an overwrap in combination with a packaged deoxygenated hemoglobin blood substitute. Therefore, Applicant's claimed invention meets the requirements of novelty and inventive step over references D1 through D6.

Certain Defects in the International Application

The Examiner stated that much of the description of the present demand is concerned with the preparation of the blood substitute and, because the claims are directed to the package itself, portions of the demand that do not pertain to the claimed subject matter must be excised from the description.

Applicant acknowledges the Examiner's observation and will amend the specification, as necessary, at the national stage.

SUMMARY AND CONCLUSIONS

For the reasons stated above, Applicant believes that the subject-matter of each of the claims is novel and includes an inventive step, thereby satisfying the requirements of PCT Articles 33(2) and 33(3). Accordingly, Applicant respectfully requests an affirmative statement under PCT Article 35(2) from the International Preliminary Examining Authority with respect to all of the attached claims.

Respectfully submitted,

HAMILTON, BROOK, SMITH & REYNOLDS, P.C.

By_____
N. Scott Pierce
Registration No. 34,900
Telephone: (781) 861-6240
Facsimile: (781) 861-9540

Lexington, Massachusetts 02421-4799
Dated: 7/25/01

CLAIMS

The invention claimed is:

1. A method for preserving a packaged deoxygenated hemoglobin blood substitute comprising maintaining the packaged deoxygenated hemoglobin blood substitute in an oxygen barrier film overwrap package including a transparent laminate material, the transparent laminate material comprising a polyolefin layer and an oxygen barrier layer that includes ethylene vinyl alcohol, wherein the laminate has a thickness of between about 0.0254 and 0.254 millimeters, and an oxygen permeability of less than about 0.01 cubic centimeters per 645 square centimeters over 24 hours at one atmosphere and at about 23°C.

2. The method of Claim 1, wherein the polyolefin layer and the oxygen barrier layer are co-extruded.

3. The method of Claim 1, wherein the oxygen barrier film overwrap package comprises at least two sheets of laminate material, wherein at least one sheet of the overwrap package comprises transparent laminate material and wherein at least one other sheet of the overwrap package comprises a foil laminate material.

4. The method of Claim 3, wherein the overwrap package is produced by:
   a) forming said foil laminate to define at least one chamber;
   b) placing the deoxygenated hemoglobin blood substitute into said chamber; and
   c) heat sealing the transparent laminate to the foil laminate, whereby said oxygen barrier film overwrap is formed, thereby containing the hemoglobin blood substitute within the overwrap.

5. The method of Claim 1, wherein the hemoglobin blood substitute is maintained under a nitrogen, argon or helium atmosphere.

6. A preserved deoxygenated hemoglobin blood substitute, comprising:
   a) a packaged deoxygenated hemoglobin blood substitute; and
   b) an oxygen barrier film overwrap package comprising a transparent laminate material, the transparent laminate material comprising a polyolefin layer and an oxygen barrier layer that includes ethylene vinyl alcohol, wherein the laminate has an oxygen permeability of less than about 0.01 cubic centimeters per 645 square centimeters over 24 hours at one atmosphere and at about 23°C, wherein the packaged deoxygenated hemoglobin blood substitute is sealed within the overwrap package.

7. The preserved deoxygenated blood substitute of Claim 6, wherein the first polyolefin layer and the oxygen barrier layer are co-extruded.

8. The preserved deoxygenated blood substitute of Claim 6, wherein the oxygen barrier film overwrap package comprises at least two sheets of laminate material, wherein at least one sheet of the overwrap package comprises transparent laminate material and wherein at least one other sheet of the overwrap comprises a foil laminate material.

9. The preserved deoxygenated blood substitute of Claim 8, wherein the overwrap package is produced by:
   a) forming said foil laminate to define at least one chamber;
   b) placing the packaged deoxygenated hemoglobin blood substitute into said chamber; and
   c) heat sealing the transparent laminate to the foil laminate, whereby said oxygen barrier film overwrap is formed, thereby containing the packaged hemoglobin blood substitute within the overwrap.